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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/218,660	12/22/98	UNGER	UNGR-1520

EXAMINER	
SHABAREH, S	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 09/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/218,660	UNGER ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100,102,103,113,115,122,124,127,194-200,203,210-238,245-248,255-270,277-280,287-292,294-300,303 and 310-329* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14-16,19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 100,102,103,113,115,122,124,127,194-200,203,210-238,245-248,255-270,277-280,287-292,294-300,303,310-329,331-337 and 347-411.

DETAILED ACTION

Amendment filed on January 18, 2001 has been entered. Accordingly, claims 101, 114, 123, 201, 202, 204-209, 239-244, 249-254, 271-276, 281-286, 293, 301-302, 304-309, 330, 338-346 have been canceled, and claims 357-411 have been added. Claims 100, 102-103, 113, 115, 122, 124, 127, 194-200, 203, 210-238, 245-248, 255-270, 277-280, 287-292, 294-300, 303, 310-329, 331-337, 347-411 are now pending.

Applicant is requested to provide a set of all pending claims in response to this Office Action.

Priority

1. Applicant's arguments with respect to the priority ruling have been fully considered and are found persuasive. The effective priority date used for the examination of the instant application is May 1, 1996.

Response to Arguments

Any previously made rejection that is not addressed in this Office Action is considered to be obviated in view of amendments filed on January 18, 2001.

Claims 100, 102, 127, 194, 203, 294, 303, 320-338 stand rejected under 35 U.S.C. 102(e) as being anticipated by Lanza et al US Patent 5,989,520.

Applicant's arguments with respect to the rejection over Lanza has been fully considered and were found partially persuasive, accordingly the rejection is now directed to claim 100, 102, 127, 194, 203, 294, 303, 320-338.

Applicant's argues that Lanza does not teach targeting ligands bound to the lipid vesicle via a hydrophilic polymer-linking group.

In response, Examiner states that Lanza specifically discloses using a polymerized lipid linked or a lipid with ether or ester linked fatty acids (col. 5, lines 60-65). Moreover, Lanza states that his ligand may be also conjugated to the emulsion directly or indirectly through intervening chemical groups or conjugated directly or indirectly to biotin or analog thereof via a spacer molecule (col 6, lines 50-68, col 10, lines 1-10). Specifically Lanza states that direct conjugation of ligand to a perflurocarbon emulsion is not preferred (col 7. lines 13-16). As discussed previously, Lanza et al disclose liposomal compositions comprising a perfluorocarbon gas, a bioactive agent, a phospholipid wall, and a targeting moiety (see col 5-7, specifically col 7 lines 41-52, examples 1-4.) Lanza also disclose the use of various suitable therapeutic agents, such as streptokinase, or gene therapy delivery system combined with ultrasonic imaging, as well as the methods of preparing and using thereof (see col 7 lines 19-41, and lines 60-68, example 18). Finally, Lanza has the effective priority date of June 8, 1995 because all its teachings are adequately supported in its parent application 08/488,743, now US Patent 5,690,907. Accordingly, Lanza anticipates the instant claims.

New Grounds of Rej ction

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 113, 115, 122, 124, 261, 262, 268, 229, 236, 351, 357-382, 377, 403-411 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 113, 122, 351, 357 the use of transitional phrase "comprise" in recitations "wherein said targeting agent... comprise the sequence Lys-Gln-Ala-Gly-Asp-Val" is ambiguous and vague, because the metes and bounds of the claim with respect to the targeting moiety is not clear. Specifically, it is not clear what is the targeting moiety that applicant is claiming as the invention. The recitation appears to be in improper markush format because said chain can existed in variety of polypeptide chains the properties of which can be distinct. Accordingly, Examiner suggests the use of "is" in replace of "comprise" to better define the scope of the claim.

Claims 377, 403 recites the limitation "said receptors" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claims 100, 102-103, 113, 115, 122, 124, 127, 194-200, 203, 210-238, 245-248, 255-270, 277-280, 287-292, 294-300, 303, 310-329, 331-337, 347-411 are rejected under 35 U.S.C. 103(a) as being unpatentable over Porter US Patent 5,648,098 in view of Lanza et al 5,989,520 and Konigsberg et al US Patent 5,258,499 or Trubetskoy et al

(Biochemica et Biopysica Acta 1131 (1992) 311-313); and Ginsberg US Patent 5,656,442 and Siegel et al US Patent 5,695,460.

Porter teaches enhanced thromolytic activity when a perfluorinated micro bubble is used in combination with a thrombolytic agent. Porter however fails to teach the use of a lipid vesicle encapsulating a perfluorocarbon.

Lanza is primarily used to show that liposomes containing perfluorinated emulsions provide improved targeting specificity when they are attached to a targeting ligand (abstract). However, Lanza fails to specifically use a polypeptide targeting having a sequence Lys-Gln-Ala-Gly-Asp-Val as set forth in claims 113, 357, 383 and their respective dependent claims.

The concept of enhancing liposomal specificity by conjugating liposomes to a ligand such as a peptide, a lipid, or a nucleic acid is well known in the art and has also been described by Lanza et al US Patent 5,989,520, the teaching of which is discussed above. Furthermore, it is well known in the art how to modify carriers such that they are bound, ionically or covalently, to a ligand that binds to a cell surface receptor. For example, Konigsberg et al in US 528,499 describes the incorporation of receptor specific ligands into Liposomes, which are then used to target receptors on the cell surface. Similarly, Trubetskoy teaches how one of ordinary skill in the art is capable of preparing a targeted cationic liposomes via an ionic bridge between two cationic

moieties. Therefore, it is well settled in the art that preparing targeting Liposomes to create more specific delivery systems is conventional.

Ginsberg discloses the synthetic alpha-amino acid containing chains of Lys-Gln-Ala-Gly-Asp-Val or RGD (col 33, lines 45-55) that are to specifically bind to fibrinogen of the platelet membrane glycoprotein complex IIb/IIIa receptor and can be used as a targeting ligand in an *in vitro* kit (abstract).

Siegel et al discloses methods of utilizing a combination of ultrasonic energy and a liposomal contrast agent to enhance thrombolytic activity of a thrombolytic agent (abstract). Siegel used Echogen which is a per fluorocarbon containing liposomal formulation (see col 5, lines 50-55). Accordingly, Siegel addresses the limitations set forth in claims 383 as directed to process steps. Siegels liposomes however do not have a targeting agent.

The teachings of all cited art are viewed as being in the same field of endeavor, because they provide general knowledge in the area of Sonotherapy and targeted liposomal formulations.

Although Porter does not specifically use a targeting agent to improve the specificity of his vesicles, it would have been obvious to one of ordinary skill in the art at the time of invention to practice Porters methods with lipid vesicles of Lanza, and further conjugate the targeting agents of Ginsberg to such lipid vesicles by conventional methods, as taught by Konigsberg or Trubetskoy, and finally administer the composition

while applying an ultrasonic energy, as taught by Siegel, because the ordinary skill in the art would have had a reasonable expectation to succeed in improving the specificity and thus thrombolytic activity of conventional thrombolytic therapy. Furthermore, differences in ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such ranges (such as the instant rate of administration) is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Conclusion

No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Further, Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on January 13, 2001 has also prompted the new ground(s) of rejection presented in this Office action. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a)

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on 703-308-2328. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

sjs 9/9/2001

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